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ETIOLOGY CLINICAL PRESENTATION OUTCOME IN MENINGITIS IN A TERTIARY CARE HOSPITAL

Paediatrics

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KEYWORDS

Introduction

Meningitis refers to inflammation of the leptomeninges, the connective tissue layers in closest proximity to the surface of the brain. Meningitis can be caused by bacteria, viruses, parasites, and fungi as well as by non-infectious conditions including inflammatory disorders (e.g., systemic lupus erythematosis or Kawasaki disease) and neoplasia (e.g., leukemic meningitis)[1]. Meningitis due to viruses and certain other non bacterial pathogens has been designated aseptic meningitis. Bacterial meningitis including tubercular meningitis is one of the most potentially serious infections occurring in infants and older children. This infection is associated with a high rate of acute complications and risk of long-term morbidity. The etiology of bacterial meningitis and its treatment during the neonatal period (0-28 days) are generally distinct from those in older infants and children[2]. Nonetheless, the etiology of meningitis in the neonatal and post neonatal periods may overlap, especially in 1-2 mo old patients, in whom group B Streptococcus, Streptococcus pneumoniae (pneumococcus), Neisseria meningitidis (meningococcus), and Haemophilus influenzae type b all may cause meningitis. The incidence of bacterial meningitis is sufficiently high in febrile infants that it should be included in the differential diagnosis of altered mental status or other neurologic dysfunction[2].

The outcome of meningitis specially the Tubercular meningitis (TBM) is influenced by the stage of disease at the start of treatment.Regardless of etiology, most patients with acute CNS infection have similar clinical syndromes. Common symptoms include headache, nausea, vomiting, anorexia, restlessness, and irritability; however, most of these symptoms are nonspecific. Common signs of CNS infection, in addition to fever; include photophobia, neck pain and rigidity, obtundation, stupor, coma, seizures, and focal neurologic deficits [2]. Tuberculous meningitis (TBM) is affecting the children more and more and has acquired an endemic shape [3]; more so in poor socio-economic group. Incidence of TBM is 7-12% in developing countries. Tuberculous meningitis complicates about 0.3% of untreated tuberculosis infections in children [7]. It is most common in children between 6 months and 4 yr of age[4]. Rapid progression tends to occur more often in infants and young children, who can experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema[4] more commonly, the signs and symptoms progress slowly over several weeks and can be divided into 3 stages.

Material and Methods

STUDY DESIGN

Our study was a Hospital based cross-sectional, analytical design.

STUDY DUARATION:

This study was done for a period of 18 months from 1st April 2013 to 30th September 2014.

STUDY SETTINGS:

The study was conducted at Post-Graduate Department of Paediatrics, in G.B Pant Hospital, an associated hospital of Government Medical College Srinagar .The hospital is a tertiary care referral centre having catchment area of both rural and urban populations.

Objectives:

To study about aetiology, clinical presentation and outcome in meningitis of different aetiologies in tertiary care hospital.

CONSENT:

The nature and the purpose of procedure of lumbar puncture was explained to the parents/guardians. A written informed consent from parents was taken in all cases.

INCLUSION CRITERIA:

The patients fulfilling the inclusion criteria between the ages of 2 months to 12 years suspected of central nervous system infection were admitted in the study. Tubercular meningitis (TBM), Partially treated pyogenic meningitis (PTM), Aseptic meningitis (AM) and Pyogenic meningitis (PM), with each group having their own inclusion criteria.

Pyogenic meningitis (PM) group In this group, CSF of patients showing organisms in gram stained smear or culture was taken as diagnostic criteria. In the absence of organisms CSF showing pleocytosis of more than 100 cells/mm^3 predominantly polymorphs, sugar less than half of blood sugar and protein more than 60 mg % was taken as inclusion criteria.

Partially treated pyogenic meningitis (PTM) group This group consisted of patients in whom CSF showed presence of organisms on gram stained smear or culture. In the absence of organism CSF showed pleocytosis of more than 100 cells /mm^3, sugarless than half of blood sugar, protein more than 60 mg % and who had received I.V. antibiotics for pyogenic meningitis for more than 48 hours before coming to hospital.

Aseptic meningitis (AM) group This group consisted of patients whose CSF showed absence of organisms on gram stain and culture and CSF showed pleocytosis of more than 10 cells/mm^3 with predominance of lymphocytes and sugar more than 2/3 of blood sugar value.

Tuberculous meningitis (TBM) group In this group the patients had two or more of the following features including signs and symptoms of meningitis; fever for > two weeks, contact with an adult with tuberculosis, positive Montoux test. This group had CSF with absolute lymphocyte counts > 50 cells/mm3, protein more than 60 mg % and sugar less than 2/3 of blood sugar, chest X-ray showing skiagram suggestive of pulmonary TB, isolation of AFB from any site, CT scan showing evidence of chronic meningitis like hydrocephalus, basal exudates, infarcts, tuberculomas and histological evidence of tuberculosis.

The selected patients underwent a detailed history and thorough clinical examination, followed by routine laboratory investigations including CBC, CRP/ESR, Chest X-Ray, Montoux test,Serum Electrolytes (Sodium, Potassium, Chloride, and Bicarbonate), Serum Calcium, and Serum Phosphorus, Blood Sugar, Blood Culture, KFT, LFT, Abdominal and Cranial USG, CT/CECT Brain MRI Brain where Ever Indicated.

After a proper informed consent CSF sample was taken by spinal tap, after excluding any contraindication like focal neuro-deficit, taping site infection, brain tumour, hemicrainal headache, cranial nerve palsies, bleeding disorders, cardiovascular instability, raised intracranial pressure (except raised fontanels), and papilledema.

2 ml of CSF sample was collected in a sterile bottle at the time of admission. CSF was divided into 3 parts one part for chemical analysis; one for cells, gram staining, acid fast bacilli staining(AFB), culture with sensitivity; and one part for enzyme activity. Activity of ADA was assayed according to the method of Guisti [5].

Exclusion Criteria

1. Concomitant illness such as HIV/on immunosuppressive therapy.
2. Death or Discharge within 24 hours.

STASTICALANALYSIS:

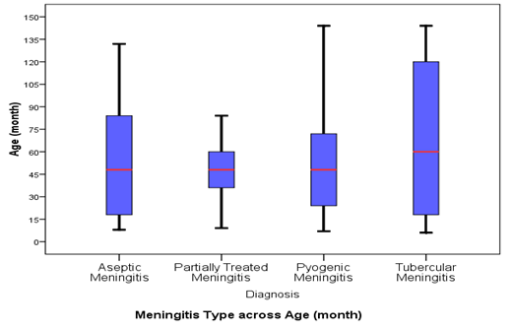
Data was entered on Microsoft Excel. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as percentages. One-way analysis of variance (One-Way ANOVA) was used to analyze mean differences among different diagnosis groups. Hochberg-GT2 was used as a multiple comparison test when group variances were similar. When group variances could not be assumed to be similar, Games-Howell was used for multiple comparisons.

Observation and Results

A total of hundred and five patients admitted during this period fulfilled the inclusion criteria. Out of 105 patients included in the study 40 cases were Aseptic Meningitis (*AM*), 21 cases Partially Treated Pyogenic - Meningitis (PTM), 29 cases Pyogenic Meningitis (PM), and 15 cases were Tubercular Meningitis (TBM). The selected patients underwent a detailed history and thorough clinical examination, followed by routine laboratory investigations.

Age	Male		Female	
	N	%	N	%
< 18 month	16	22.5	9	26.4
18 month to 3 yr	12	16.9	9	26.4
3 yr to 5 yr	12	16.9	6	17.6
5 yr to 7 yr	10	14.1	4	11.7
7 yr to 9 yr	12	16.9	3	8.8
9 yr to 12 yr	8	11.2	3	8.8
Total	71	67.1	34	32.4
Mean ± SEM	**59.6 ± 5.7 (8, 144)**		**48.7 ± 8.1 (6, 144)**	
Median	**60**		**48**	

Data was expressed as mean ± SE, median and percentages. Patients were in between 6 and 144 month age, when the mean was 56.1 ± 4.7 months and respective median was 48 months. Preponderance of 71 (67.1) males who were in between 8 and 144 month with the mean age of 59.6 ± 5.7 months, did not differ (p>0.05) from 34(32.4) females who were in between 6 and 144 month with mean age 48.7 ± 8.1 months.



Age of TBM subjects was 69.2 ± 16.7 (6, 144) months when age of Aseptic Meningitis (AM), Partially Treated Meningitis (PTM) and Pyogenic Meningitis (PM) subjects was 55.1 ± 7.8 (8, 132), 52.1 ± 8.7 (9, 144) and 53.4 ± 8.3 (7, 144) months..

Table 4- Clinical Features of the studied Meningitis Patients

	N	%
Fever	103	98.1
Vomiting	86	81.9
Headache	68	64.7
Neck Stiffness	63	60.0
Kernings	33	31.4
Altered Sensorium	22	21.4
Seizures	20	18.6
Bulging Anterior Fontanella	13.5	12.9
Irritability	7	7.1
Brudzinskis	5	4.7

Clinical features stated herewith in chronological order. Most frequent clinical feature was Fever (98.1) followed by Vomiting (81.9), Headache (64.7), Neck Stiffness (60.0), Kernings (31.4), Altered Sensorium (21.4), Seizures (18.6), bulging Anterior Fontanella (12.9), Irritability (7.1) and Brudzinskis sign (4.7).

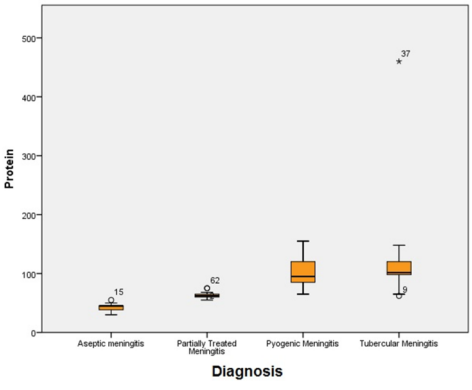
	N	Mean [cells/mm^3]	Std. Deviation	Std. Error	Minimum	Maximum
Aseptic Meningitis	40	140.89	68.145	13.114	27	280
Partially Treated pyo Meningitis	21	163.43	54.860	14.662	106	250
Pyogenic Meningitis	29	1022.00	720.485	165.291	300	2700
Tubercular Meningitis	15	748.00	676.688	213.988	170	2500

Total CSF -cytology of TBM subjects was 748.0 ± 214.0 (170, 2500) was considerably higher than that of AM 140 ± 13.114 (27, 280) and PTM 163.43 ± 15 (106, 250). Total CSF-cytology of PM1022.0 ± 165.3 (300, 2700) in comparison to TBM was not significant.

	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum
Aseptic Meningitis	40	34.44	11.956	2.301	10	50
Partially Treated pyo Meningitis	21	65.71	13.281	3.549	50	90
Pyogenic Meningitis	29	71.32	10.781	2.473	55	95
Tubercular Meningitis	15	31.00	12.867	4.069	10	45

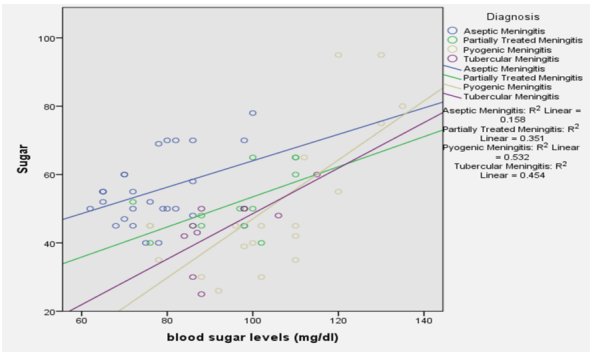
Polymorphs in CSF cytology of TBM subjects 31.0% ± 4.1 (10, 45) was considerably lower than that of AM 34.44% ± 2.3 (10, 50), PTM 65.71% ± 3.549 (50, 90), PM 71.32% ± 2.47.TBM in comparison to AM was not significant. Otherwise the difference was significant.

	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum
Aseptic Meningitis	40	65.19	11.476	2.209	50	90
Partially Treated pyo Meningitis	21	34.29	13.281	3.549	10	50
Pyogenic Meningitis	29	28.68	10.781	2.473	5	45
Tubercular Meningitis	15	69.00	12.867	4.069	55	90



Box plot showing meningitis type across proteins in CSF

Protein level of TBM subjects 136.4 ± 36.8 (62, 460) was significantly higher than that of AM 42.48 ± 1.193(30, 55) and PTM 63.43± 1.6(55, 75) PM 101.05 ± 5.992 (65, 155) or all the Non-TBM 70.0 ± 3.6 (30, 155) subjects



Discussion

Routine CSF laboratory parameters may not be helpful to differentiate TBM from other meningitis like partially treated pyogenic meningitis and aseptic meningitis. Demonstration or isolation of acid-fast bacilli on CSF smear or culturing of Mycobacterium which takes 4-6 weeks to show the growth is usually difficult[10]. Organisms may be recovered in culture of large volumes of CSF[4,9] and in bacterial meningitis when patient comes after a course of antibiotics, organisms are usually not isolated.CSF cytology, biochemistry are other means to confirm the aetiology but again, the results may overlap.

A total of seventy patients admitted during this period fulfilled the inclusion criteria. Out of 105 patients included in the study 40 cases were Aseptic Meningitis (AM), 21 cases partially treated pyo-meningitis (PTM), 29 cases pyogenic meningitis (PM) and 15 cases were tubercular meningitis (TBM). Patients were in between 6 and 144 months of age. Preponderance of 71(67.2) males who were in between 8 and 144 month with the mean age of 59.6±5.7 months, did not differ (p>0.05) from 34(32.4) females who were in between 6 and 144 month with mean age 48.7±8.1 months.

The common clinical presentations of meningitis observed in our study was Fever (98.1) followed by Vomiting (81.9), Headache (64.7), Neck Stiffness (60.0), Kernings (31.4), Altered Sensorium (21.4), Seizures (18.6), bulging Anterior Fontanella (12.9), Irritability (7.1) and Brudzinskis sign (4.7).Similar clinical presentations were also noted by *Rajesh Baheti et al* and Malla K et al but with different frequencies[8,14].

Mycobacterium couldn't be isolated in any of the TBM cases which differed from two studies of Gupta B K et al 6/29[12] and Pan A et al 1/32[14]however was consistent with Malla K et al 0/10[16].

In our study in 12 out of 29 cases of pyogenic meningitis organisms were isolated from CSF culture, which included Streptococcus pneumoniae in 6 cases H influenza in 3 cases and Staphylococcus aureus in 2 cases and N meningitides in 1 case. Whereas in a study carried by Rana SV et al[9] organisms were isolated from CSF culture in 4 patients out of 10 cases of pyogenic meningitis [PM] and Pan A et al 2/13[13].Bacterial isolates in CSF in our study were quite similar in relation with some other studies [9, 12,13,14]. Although Hib is the commonest causative agent, with the availability of Hib conjugate vaccine, the current likely hood of Hib meningitis in a child who has received at least two doses of vaccine was extremely rare. *S.pneumoniae was most commonly isolated pathogenon CSF culture as in a study carried by Thomas V et al[20]* .

The CSF total count (1022.0 ±165.3) and neutrophil count (71.32± 2.47) in pyogenic meningitis was highest. CSF Sugar was lowest (35.344) while the CSF Lymphocyte (69.0±4.1) and Protein (136.4±36.8) were highest in TBM. Rana SV et al[9] and Pan A et al[13] study groups pyogenic meningitis had the highest mean cell counts and TBM group had the highest mean protein values. Malla K et al [14] analysed the CSF total count (903.28±1419.73) and neutrophil count (84.18±12.26) in PM was highest. CSF Sugar was lowest (29.15±15.11) in PM while the CSF Lymphocyte (90.60±8.11) and Protein (256.90±203.61) were highest in TBM, These results are comparable to our study. These significant parameters may be additional supporting investigations to further differentiate different types of meningitis.

The mean level of ADA in our study was 30.0±3.2 (20.0, 54.0) among Tubercular Meningitis (TBM) cases. Its respective levels among Aseptic Meningitis (AM) was 8.1±0.3 (4.0, 11.5), Partially Treated Pyogenic Meningitis (PTM) was 7.6±0.4 (5.0, 11.0), Pyogenic Meningitis (PM) was 11.6±0.5 (8.0, 14.5) .

Rana SV et al [9] in their analysis found mean ±SE ADA levels in Tubercular meningitis (TBM) of 18.22±3.35 (1.0-96.7), partially treated pyogenic meningitis (PTM) 6.28±0.91 (3.0-11.1), pyogenic meningitis (PM) 7.98±3.56 (0.3-29.0), Aseptic Meningitis (AM) 3.43±0.86 (0.1-08.5), This difference of ADA values in CSF between TBM and other types of meningitis was statistically significant (p<0.01) which is comparable with our study .

Gupta B K et al[15] in their analysis found that tuberculous group ADA activity in CSF ranged between 9.2 to 110 U/L with a median of 22, mean ±SD as 27.1684±22.4563while in non-tuberculous group ADA activity ranged between 2 to 10.5 U/L with a median of 6, mean±SD as 6.0619±2.5399, which is comparable with our study.

The sensitivity and specificity of CSF ADA at a cut off 10 IU/L in our study was 100% and 66.67%, negative predictive value 100%, diagnostic accuracy of 71.43%.Other studies have shown sensitivity ranges of 44-100% and specificities of 75-99% for total ADA (by using 8 to 20 IU/L as cut off value for diagnosis[7,16,17,].The sensitivity, negative predictive and diagnostic accuracy value of CSF-ADA for TBM increased if the cut off value was increased without changing the specificity in our study group. Out of 15 cases of TBM BCG scar was present in 4 patients .Montoux was positive in 8 out of 15 patient in TBM.TB PCR in CSF was positive for TB in 7 patients. Almost all patients with TBM had features TBM on CT and MRI which included basal effacement in all cases of TBM, basal exudates 7 patients of TBM(46.6%) ,infarcts in 5(33.33%) and tuberculomas in 3(20 %).Family history of tuberculosis was present in 9 Out of 15 cases of TBM.

Most patients with PM and PTM recovered with ceftriaxone for period of 10 to 14 days.7 patients of PM required ICU admission varying from 2 days to 5 days.3 patients with PM required IPPV. Patients with culture proven Streptococcus and Staphylococcus were supplemented with vancomycin for 2 weeks. Patients with AM were treated symptomatically along with injectable ceftriaxone for no more than 10 days and Acyclovir was added in 8 patients with features of HSV meningo encephalitis which included positive HSV PCR in 5 patients. All patients with PM, PTM, AM were discharged but 3 patients had hearing sequelae in PM group and 1 patient with HSV AM had residual ataxia.

All patients with TBM were treated by ATT for a period of 18 months. 10 patients with TBM were diagnosed in stage 2. 3 in stage 3 with significant residual sequelae needed vocational and functional rehabilitation.

Summary and Conclusion

- The study was conducted in G.B Pant Hospital, Postgraduate Department of Paediatrics, an associated hospital of Government Medical College Srinagar, referral tertiary care hospital for the children of Kashmir valley.This study was conducted over a period of 18 months from 1st April 2013 to 30TH 2014.
- A total of 105 patients admitted during this period fulfilled the inclusion criteria which included 40 cases of Aseptic Meningitis (AM), 21 cases Partially Treated Pyo-Meningitis (PTM), 29 cases Pyogenic Meningitis (PM), and 15 cases were Tubercular Meningitis (TBM). Preponderance of 71(67.2%) males with the mean age of 59.6±5.7 months, did not differ (p>0.05) from 34(32.4%) females with mean age 48.7±8.1 months. Mean age of TBM subjects was 69.2±16.7 months when age of Aseptic Meningitis (AM), Partially Treated Meningitis (PTM) and Pyogenic Meningitis (PM) subjects was 55.1 ±7.8, 52.1±8.7 and 53.4±8.3 months.
- Most frequent clinical feature observed in our study was Fever (98.1) followed by Vomiting (81.9), Headache (64.7), The CSF total count (1022.0 ± 165.3) and neutrophil count (71.32±2.47) in Pyogenic meningitis was highest. CSF Sugar was lowest (35.344) while the CSF Lymphocyte (69.0±4.1) and Protein (136.4 ± 36.8) were highest in TBM
- In our study we observed a significant high level of ADA 30.0± 3.2U/L (20.0, 54.0) among the tubercular meningitis (TBM) patients and its respective level among Aseptic Meningitis (*AM*), was 8.1± 0.3U/L(4.0, 11.5), partially treated pyo -meningitis

(PTM) was 7.6 ± 0.4U/L (5.0, 11.0), pyogenic meningitis (PM) was 11.6±0.5U/L (8.0, 14.5).

- Most patients with PM and PTM recovered with injectable ceftriaxone for period of 10 to 14 days.7 patients of PM required ICU admission varying from 2 days to 5 days.3 patients with PM required IPPV. Patients with culture proven Streptococcus and Staphylococcus were supplemented with vancomycin for 2 weeks. Patients with VM were treated symptomatically along with injectable ceftriaxone for no more than 10 days and Acyclovir was added in 8 patients with features of HSV meningo encephalitis which included positive HSV PCR in 5 patients. All patients with PM, PTM, VM were discharged but 3 patients had hearing sequelae in PM group and 1 patient with HSV VM had residual ataxia.

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